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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
MCKENZIE, THOMAS C

ART UNIT	PAPER NUMBER
1624	12

DATE MAILED: 12/30/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/762,106	BROWN ET AL.	
	Examiner	Art Unit	
	Thomas McKenzie Ph.D.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period f r Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 November 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5,6,8-10 and 12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,6,9,10 and 12* is/are rejected.

7)☒ Claim(s) *8* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *11* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to amendments filed on 11/6/02. Applicants amended claims 2, 8, and 12. All claims were previously rejected. Claims 1-3, 5, 6, and 8 are compound claims. Claim 10 is a composition claim. Claim 12 is a use claim. Claim 9 is a synthesis claim. This is the second action on the merits. The application concerns some amidobenzamide compounds, compositions, and uses thereof.

Information Disclosure Statement

2. Applicants' comment concerning the PTO-1449 forms is noted. A form dated February 2, 2001 was located in the file. The other two forms noted by Applicants have not been found.

Title

3. Applicants' comments regarding the new procedure concerning abstracts in Rule 371 applications as outlined in MPEP §1893.03(e) are noted. Applicant is correct and no separate abstract is now required. The Examiner thanks Applicants for pointing this out. At least there can be no printer rush with the replacement abstract in the present application.

Response to Amendments and Arguments

4. Applicants' new title and abstract overcome the objections made in points #2 and #3 of the previous office action. Applicants' amendments to claims 2 and 8 removing reference to Q radicals other than phenyl overcomes the indefiniteness

rejections made in points #5 and #6. Applicants' arguments concerning the written description rejection concerning "*in-vivo* cleavable ester" and made in point #8 are persuasive. The level of experimentation required is not a factor for written description. While the Examiner asserts that Applicants do not have description of esters in addition to those described in lines 4-13, page 23 that issue is so closely tied to the indefiniteness rejection below that the written description rejection would be cumulative. Any argument or amendment that would overcome one rejection would necessarily overcome the other. Thus, the written description rejection made in point #8 is withdrawn. Applicants' argument concerning the proviso and the art rejection over Ashton, (J. Med. Chem.) is persuasive. Thus, the anticipation rejection made in point #10 is withdrawn.

Claim Rejections - 35 USC § 112

5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Claims 1-3, 5, 6, 9, 10, and 12 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "*in-vivo* cleavable ester" in claims 1, 6, 10, and 12 is indefinite. The issue on second paragraph is whether the structures of the claimed compounds are clearly defined. Applicants' "*in-vivo* cleavable ester" are molecules whose structure lie outside the subject matter of Formula I, but upon

metabolism in the body are converted to active compounds falling within the structural scope of Formula I. The phrase describes the function intended but provides no specific structural guidance to what constitutes an "*in-vivo* cleavable ester". Structural formulas, names, or both can accurately describe organic compounds, which are the subject matter of claim 1. Attempting to define means by function is not proper when the means can be clearly expressed in terms that are more precise. Lines 4-13, page 23 list suitable esters but use open language "for example". The Examiner suggests using these specific examples in the claim to clarify what Applicants' intend.

Applicants argue that prodrugs have been claimed previously in US Patents, that prodrugs are an established concept in medicinal chemistry, and that no experimentation is required to make Applicants' "*in-vivo* cleavable ester" molecules. This is not persuasive. Firstly, the "prodrug" feature upon which applicant relies is not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Secondly, although the Examiner has not searched the US Patent database for the term "*in-vivo* cleavable ester", the indefiniteness would remain despite what

was allowed in another case. The U.S. Court of Customs and Patent Appeals wrote *In re Giolito* 188 USPQ 645: "We reject appellants' argument that the instant claims are allowable because similar claims have been allowed in a patent. It is immaterial whether similar claims have been allowed to others. See *In re Margaroli,* 50 CCPA 1400, 318 F.2d 348, 138 USPQ 158 (1963); *In re Wright*, 45 CCPA 1005, 256 F.2d 583, 118 USPQ 287 (1958); *In re Launder*, 41 CCPA 887, 212 F.2d 603, 101 USPQ 391 (1954)".

Thirdly, the Examiner agrees that synthesis of the esters listed in lines 4-13, page 23 from carboxyl containing molecules of Formula (I) would be a routine exercise for the average medicinal chemist. However, what about the claimed esters not listed in the passage cited above? Since the structures of these "*in-vivo* cleavable ester" molecules are uncertain, direction for their preparation must be even more unclear.

6. Claim 12 remains rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim provide for the use of the compounds of formula I, but the claims do not set forth any steps involved in determining what is "a disease or medical condition mediated by a cytokine". It is unclear what diseases and treatments applicant is intending to encompass. A claim

is indefinite where it merely recites a use without any active, positive steps delimiting how to practice this use. Identifying which diseases applicants intend this claim to cover will involve extensive and potentially inconclusive clinical research. With out such clinical research to identify the patients and diseases applicants intend to treat, one skilled in the art cannot determine the metes and bounds of the claim.

Applicants cite the utility training guidelines and argue that no steps are required to practice their invention of disease treatment. This is not persuasive for three reasons. Firstly, the rejection was indefiniteness, made under 35 U.S.C. 112 not a utility rejection made under 35 U.S.C. 101. Secondly, the critical step required to practice Applicants use is identification of the symptoms and patients Applicant intend to treat. Determining whether a given disease responds or does not respond to such a cytokine production inhibitor and thus, covered by the claim language, will require extensive and potentially inconclusive clinical research. Suppose that a given drug, which exhibits cytokine production inhibitor properties *in vitro*, when administered to a patient with a certain disease, does not produce a favorable response. One cannot conclude that specific disease does not fall within this claim. Keep in mind that:

A. It may be that the next patient will respond. No pharmaceutical has 100% efficacy. What success rate is required to conclude our drug is a treatment? Thus, how many patients need to be treated? If "successful treatment" is what is intended, what criterion is to be used? If one person in 10 responds to a given drug, does that mean that the disease is treatable? One in 100? 1,000? 10,000? Will the standard vary depending on the current therapy for the disease?

B. It may be that the wrong dosage or dosage regimen was employed. Drugs with similar chemical structures can have markedly different pharmacokinetics and metabolic fates. It is quite common for pharmaceuticals to work and or be safe at one dosage, but not at another that is significantly higher or lower. Furthermore, the dosage regimen may be vital --- should the drug be given e.g. once a day, or four times in divided dosages? The optimum route of administration cannot be predicted in advance. Should our drug be given as a bolus *iv* or in a time-release *po* formulation. Thus, how many dosages and dosage regimens must be tried before one is certain that our drug is not a treatment for this specific disease?

C. It may be that our specific drug, while active *in vitro*, simply is not potent enough or produces such low concentrations in the blood that it is not an effective treatment of the specific disease. Perhaps a structurally related drug is potent

enough or produces high enough blood concentrations to treat the disease in question, so that the first drug really does fall within the claim. Thus, how many different structurally related cytokine production inhibitors must be tried before one concludes that a specific compound does not fall within the claim?

D. Conversely, if the disease responds to our second drug but not to the first, both of whom are cytokine production inhibitors *in vitro*, can one really conclude that the disease falls within the claim? It may be that the first compound result is giving the accurate answer, and that the success of second compound arises from some other unknown property that the second drug is capable. It is common for a drug, particularly in the CNS, to work by many mechanisms. The history of psychopharmacology is filled with drugs, which were claimed to be a pure receptor XYX agonist or antagonist, but upon further experimentation shown to effect a variety of biological targets. In fact, the development of a drug for a specific disease and the determination of its biological site of action usually precede linking that site of action with the disease. Thus, when mixed results are obtained, how many more drugs need be tested?

E. Suppose that our drug is an effective treatment of the disease of interest, but only when combined with some very different drug. There are for example,

agents in antiviral and anticancer chemotherapy that are not themselves effective, but are effective treatments when the agents are combined with something else.

Consequently, determining the true scope of the claim will involve extensive and potentially inconclusive research. Without it, one skilled in the art cannot determine the actual scope of the claim. Hence, the claim is indefinite.

Thirdly, Cytokines are extraordinarily diverse in their structure and function. The term cytokine is used as a generic name for a diverse group of soluble proteins and peptides, which act as humoral regulators and which, either under normal or pathological conditions, modulate the functional activities of individual cells and tissues. As for structure, most Cytokines are unrelated in terms of sequence.

7. Claim 12 remains rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of rheumatoid arthritis and psoriasis, does not reasonably provide enablement for every "disease or medical condition mediated by a cytokine". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. English (Trends) in figure 1, page 42 summarizes in which diseases clinical trials have started for other p38 enzyme inhibitors, which is the postulated mechanism of action of Applicants compounds.

Applicants again point to the training materials concerning utility and assert that similar styled claims have been previously allowed. This is not persuasive for three reasons. Firstly, the rejection was scope of enablement, made under 35 U.S.C. 112 not a utility rejection made under 35 U.S.C. 101. Secondly, the scope of "cytokine" cannot be deemed enabled. Cytokines proteins mediate interactions between cells directly and regulate processes taking place in the extracellular environment. In general Cytokines act on a wider spectrum of target cells even than hormones and, unlike hormones, Cytokines are not produced by specialized cells which are organized in specialized glands, i.e. there is not a single organ source for these mediators. The fact that cytokines are secreted proteins also means that the sites of their expression do not necessarily predict the sites at which they exert their biological function.

Almost all Cytokines are pleiotropic effectors showing multiple biological activities. In addition, multiple cytokines often have overlapping activities and a single cell frequently interacts with multiple cytokines with seemingly identical responses (cross-talk). One of the consequences of this functional overlap is the observation that one factor may frequently functionally replace another factor altogether or at least partially compensate for the lack of another factor. Since most

Cytokines have ubiquitous biological activities, their physiologic significance as normal regulators of physiology is often difficult to assess.

The activities of cytokines as a group are extremely complex. Many Cytokines show stimulating or inhibitory activities and may show synergism or antagonism to the actions of other factors. A single cytokine may elicit reactions also under certain circumstances that are the reverse of those shown under other circumstances. The type, the duration, and also the extent of cellular activities induced by a particular cytokine can be influenced considerably by the micro-environment of a cell, depending, for example, on the growth state of the cells (sparse or confluent), the type of neighboring cells, cytokine concentrations, the combination of other Cytokines present at the same time, and even on the temporal sequence of several Cytokines acting on the same cell. The responses elicited by Cytokines are therefore contextual and the "informational content", i.e. the intrinsic activities of a given cytokine may vary with conditions.

Some attempts have been made to organize cytokines along lines of function, which show the tremendous variety of what is covered by “cytokine”. For example, one category is chemokines, a generic name given to a family of pro-inflammatory activation-inducible Cytokines. These include a) SIS family such as SIS-alpha, SIS-gamma and SIS-epsilon, b) SIG family including JE, KC, MGSA

(melanoma growth stimulatory activity), PF4 (platelet factor-4), PBP (platelet basic protein), LDCF (lymphocyte-derived chemotactic factor), RANTES, and SMC-CF, c) SCY family including SCY A1, SCY A2, SCY A3, SCY A4, SCY A5, SCY A6, SCY A7, SCY A8, SCY A9, SCY A10, SCY A11, SCY A12, SCYA13, SCY A14, SCY A15, SCY A16, SCY A17, SCY A18, SCY A19, SCY A20, SCY A21, SCY A22, SCY A23, SCY A24, SCY A25,SCY A26 and many others as well.

Another category is Motogenic cytokines, a category Cytokines that influence the motility and migration of cells in ways other than affected by chemotactic processes. The collective term is an functional definition and there is no structural basis that would allow different factors to be classified as motogenic cytokines. Examples include AAMP (Angio-associated migratory cell protein), Adrenomedullin, AMF (autocrine motility factor), ATX (autotaxin), B16-F1 melanoma autocrine motility factor, DF (dissociation factor), Epitaxin, FDMF (fibroblast-derived motility factor), FMSF [fibroblast motility-stimulating factor] ISF (invasion stimulating factor), Ladsin, Monocyte-derived scattering factor, MSF (migration stimulating factor), PDMF (pancreatic cancer-derived motility factor), SF (scatter factor), SFL (scatter factor-like), and Vitronectin.

Another category is the B-cell growth factor (BCGF), which includes CD23, IL1, IL2, IL4, IL5, IL6, IFN-gamma, TNF-alpha and TNF-beta.

Another type are the colony stimulating factors, which regulate white blood cell production and orchestrate the control of the growth and differentiation of bone marrow progenitor cells. These include M-CSF (macrophage-specific), G-CSF (granulocyte-specific), GM-CSF (macrophage/granulocyte-specific), IL3 (multifunctional), IL-7 and Stem Cell Factor (SCF) and MEG-CSA (megakaryocyte-specific).

A large category of cytokines is the angiogenisis factors, which include aFGF, ANF, Angiogenin, Angiotropin, AtT20-ECGF, B61, bFGF, CAM-RF, ChDI, CLAF, ECGF, ECI, EDMF, EGF, EMAP, Neurothelin, Endostatin, Endothelial cell growth inhibitor, Endothelial cell-viability maintaining factor, Epo, FGF-5, IGF-2, HBNF, HGF, HUAF, IFN-gamma, IL1, K-FGF, LIF, MD-ECI, MECIF, Oncostatin M, PD-ECGF, PDGF, PF4, PlGF, Prolactin, TNF-alpha, TNF-beta, Transferrin, VEGF, and others.

There are many, many other cytokines, including IL10, IL12, IL9, IP-10, GRO, and 9E3.

In view of the considerable diversity of structure and function, the idea that a single compound, let alone a genus of millions, could affect cytokines, or activities

regulated by cytokines, generally is contrary to what is known about these. No such compound has ever been found, and given what is already known about the diversity of such agents, there is no reason to think a compound could act generally against cytokines.

Thirdly, the how to use portion of the statute means that Applicants must teach the skilled practitioner, in this case a physician, how to treat the claimed disease. The rejected claims are drawn to treatment of "disease or medical condition mediated by a cytokine", which as recited reads on the treatment of any and all diseases for which there is no enabling disclosure. This scope of disease treatment is not adequately supported based solely on the testing data provided in the specification at pages 42-47. The specification at pages 1 and 2 asserts that the compounds are useful for treating all sorts of diseases for which Applicants have provided no empirical support. A recent review of English (Trends) cited in the prior action states that use of such p38 enzyme inhibitors is still in the experimental stage and is speculative in nature. See also Boehm (Exp. Opin. Ther. Patents) final sentence, page 34. Substantiation of use and scope is required when the use is "speculative", "sufficiently unusual", or not provided in the specification, *Ex parte Jovanovics,* 211 USPQ 907, *In re Langer,* 183 USPQ 288, *Hoffman v. Klaus*, 9 USPQ2d 1657, and *Ex parte Powers*, 200 USPQ 925 concerning the type

of testing needed to support *in vivo* use claims. Also see the MPEP § 2164.03 for enablement requirements in the structure sensitive arts of pharmacology and medicinal chemistry.

Applicants will receive patent protection for their compounds. At issue here is further protection for uses of their compounds. In a dissent to *In re MOUREU AND CHOVIN*, 145 USPQ 452, by Judge Smith he wrote "[c]learly as to the claimed chemical compound appellants here have satisfied such a requirement. They have not claimed a method of treating a disease. Why therefore should they be required to prescribe dosages, methods of administration, etc. on the theory that their invention resides in the use of rather than in the compound itself?" The answer to Judge Smith's question is that the present Applicants are doing exactly that.

Allowable Subject Matter

8. Claim 8 is objected to as being dependent upon a rejected base claim.

Conclusion

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened

statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

10. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose telephone number is (703) 308-9806. The FAX number for after final amendments is (703) 872-9307. The Examiner is available from 8:30 to 5:30, Monday through Friday. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Mukund Shah can be reached on (703) 308-4716. Please direct general inquiries or any inquiry relating to the status of this application to the receptionist whose telephone number is (703) 308-1235.

Mukund Shah
Supervisory Patent Examiner
Art Unit 1624

TCMcK
December 24, 2002

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